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**The effect of continuous positive airway pressure on blood pressure
variability in patients with obstructive sleep apnoea**

Martino F. Pengo^{1,2,3}, Culadeeban Ratneswaran¹, Marc Berry¹, Brian D. Kent¹,
Malcolm Kohler⁴, Gian Paolo Rossi², Joerg Steier^{1,3}.

1 Guy's and St Thomas' NHS Foundation Trust, Lane Fox Respiratory Unit /
Sleep Disorders Centre, London, United Kingdom,

2 Department of Medicine (DIMED), University of Padua, Italy,

3 King's College London, Faculty of Life Sciences and Medicine, United
Kingdom.

4 Department of Pneumology, University Hospital of Zurich and Center for
Interdisciplinary Sleep Research, University of Zurich, Switzerland

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Corresponding author:

Dr Martino F Pengo
Guy's & St Thomas' NHS Foundation Trust
Sleep Disorders Centre,
Nuffield house
Great Maze Pond
London SE1 9RT
Mail: martino.pengo@gstt.nhs.uk

ABSTRACT

Obstructive sleep apnoea (OSA) is a common risk factor for cardiovascular disease. Continuous positive airway pressure (CPAP) improves OSA symptoms and blood pressure control. The effect of CPAP on blood pressure variability (BPV) in patients with and without hypertension treated with auto-titrating CPAP (APAP) for two weeks was studied. 78 participants (76.9% male, 49% hypertensive, mean body-mass-index (BMI) 36.2(6.9)kg/m², age 49.0(12.9)years) underwent two weeks of APAP therapy. Office blood pressure (BP), blood pressure variability (BPV; standard deviation of three BP measurements) and pulse rate were measured before and after treatment. Systolic BPV (5.3±4.9 vs 4.2±3.4mmHg, p=0.047) and pulse rate (78.0±14.5 vs 75.5±15.8bpm, p=0.032) decreased after treatment, particularly in hypertensive participants. Mask leak was independently associated with reduced changes in systolic BPV (r=-0.237, p=0.048). Short-term APAP treatment reduced BPV and pulse rate, particularly in hypertensive patients with OSA.

BACKGROUND

Obstructive sleep apnoea (OSA) is a well-recognised risk factor for cardiovascular disease (1). Its prevalence is rising due to the current obesity epidemic (2). OSA is caused by recurrent obstructions of the upper airway when asleep, resulting in apnoeas and hypopnoeas which lead to repeated oxygen desaturations, arousals from sleep, and activation of the sympathetic nervous system (3). Increased sympathetic tone impacts on blood pressure (BP), heart rate (4) and importantly on the risk of cardiovascular morbidity.

Continuous positive airway pressure (CPAP) is an effective treatment to maintain upper airway patency and abolish or reduce obstructive events in patients with OSA (5), it reduces the associated rise in blood pressure (6). Recent studies have revealed that optimal CPAP control reduces BP, with more marked effects in patients with resistant hypertension (7) which implies a role of the autonomic nervous system in relation to changes in blood pressure.

BP variability (BPV) is a marker of the autonomic nervous system and an independent predictor of cardiovascular morbidity and mortality (8). It is defined as the fluctuation of BP between different measurements over a defined time interval (9). Visit-to-visit BPV comparison is related to an increased risk of cardiovascular events (10,11).

Patients with OSA are known to have an increased sympathetic tone which causes an increased BPV (12,13) and leads to raised levels of absolute BP and increased risk of cardiovascular morbidity and mortality. Patients with hypertension exhibit higher BPV when compared to normotensives as expression of an enhanced sympathetic tone. (9)

We aimed to investigate how CPAP treatment modifies the risk of increased sympathetic activation, through its impact on BPV, in patients with obstructive sleep apnoea.

PATIENTS AND METHODS

Patients with a diagnosis of OSA, and who had been referred to a tertiary sleep centre (Sleep Disorder Centre, Guy's & St Thomas' Hospitals, London, UK) were enrolled in this study between June 2013 and December 2013.

OSA was diagnosed according to the National Institute of Health and Clinical Excellence (NICE) guidelines (14) with a 4% oxygen desaturation index (ODI) > 5/hour combined with excessive daytime sleepiness (ESS>10). The study was approved by the local institution's review board (2014/3081) and all patients gave written informed consent.

Hypertension was defined according to current international guidelines (15). In order to investigate any differential impact of CPAP, OSA patients were divided in two subgroups: patients with a known diagnosis of hypertension or a BP greater than 140/90 mmHg on three occasions were included in the hypertensive subgroup, and patients with BP <140/90 mmHg on three occasions were included in the normotensive subgroup.

Following baseline recording of demographic data and BP measurements patients underwent nocturnal pulse oximetry and were provided with an APAP device for home use. At two-week follow-up compliance data were obtained and BP was measured again, BPV was calculated.

Baseline assessments

At baseline, participant's age, sex, height, weight, body mass index (BMI) and Epworth sleepiness scale (ESS), as a measure of daytime sleepiness (16), were recorded.

Blood pressure and blood pressure variability

At each visit, baseline and at two-week follow-up, three blood pressure measurements were taken with 1-minute intervals, using an automatic sphygmomanometer (Mindray VS-800, Medical International Limited, Shenzhen, China). Patients were rested (>5 minutes), and seated in an upright position (17).

The average of pulse rate, systolic and diastolic BP was calculated from these readings. Systolic and diastolic range was calculated as the difference between the maximum and minimum BP values. Systolic and diastolic BPV was calculated as the standard deviation (SD) of these three measurements (18).

All data were compared between baseline and two-week follow-up (following APAP treatment), this included the change (delta) in systolic and diastolic BP range, means/average BP and SD, and the delta in pulse rate.

APAP treatment and nocturnal oximetry

Following baseline measurements, patients were issued an auto-titrating continuous positive airway pressure device (APAP, S8/S9, ResMed Ltd, Sydney, Australia) for two weeks of home use. The following compliance and treatment indices were downloaded, and calculated at the end of this period: average daily APAP usage (hours), days of APAP usage >4 hours per day (n), days of APAP usage <4 hours per day (n), percentage of days of APAP usage > 4 hours per

day (%), air leak (L/min) and the 95th percentile of APAP to control respiratory events (cmH₂O).

The primary outcome parameter was change in BPV between baseline measurements and at two-weeks of treatment. Secondary outcomes included change in pulse rate, change in absolute BP values, and comparison of these parameters in patients with and without hypertension. Lastly, we compared patients who were compliant with CPAP treatment, defined as a usage for more than 4 hours per night for at least 70% of the total days of usage, with patients who had a sub-optimal CPAP compliance to determine whether BPV changes were dependent on the treatment received.

Sample size analysis

To understand the significance of the difference found on BPV pre- and post-treatment we performed a power calculation stating a significance level (adjusted for sidedness) of 0.025, the total number of patients (78) and the obtained difference in means of 1.2 mmHg. The calculated power was 99 percent that the study would detect a difference, if the true difference between treatments is 1.2 x the standard deviation.

Statistical analysis

Data were analysed using SPSS statistics 21 (IBM, New York/NY, USA) and tested for normal distribution using the Shapiro-Wilk normality test. Normally distributed data are presented as mean (SD), and were analysed with paired and unpaired t-tests. Non-normally distributed data are presented as median (IQR), and were analysed with the Wilcoxon Rank sum test when paired, and the Mann-Whitney U test when they were unpaired.

A bivariate analysis using Pearson correlation coefficient was performed when variables were normally distributed and the Spearman correlation coefficient was chosen when variables were non-normally distributed. Where bivariate analyses revealed significant correlations with either BPV or pulse rate parameters, logistic regression analyses were employed to identify independent correlations. Age, gender, BMI, APAP compliance were considered as independent variables. A sub-analysis compared BPV in patients with optimal and sub-optimal APAP compliance. Non-normally distributed data were log-transformed prior to regression analysis and comparison. Non-normally distributed data were log-transformed to adjust for the distribution, as one of the assumptions of a regression analysis is that variables need to be normally distributed, or the scientific insights yielded by a regression model could be biased and misleading. A level of significance was defined as $p < 0.05$.

RESULTS

Baseline data

We recruited a total of 78 participants with OSA: 76.9% males, BMI 36.2 ± 6.9 kg/m², age 49.0 ± 12.9 years. At baseline, the systolic and diastolic BP was 130.9 ± 15.5 mmHg and 82.7 ± 10.4 mmHg, respectively. Nocturnal pulse oximetry data confirmed severe sleep-disordered breathing with a mean 4%ODI of 27.4 ± 19.9 x hour⁻¹ and a mean 3%ODI of 33.4 ± 20.3 x hour⁻¹, whilst average oxygen saturation was 93.9 ± 3.2 %, and baseline Epworth sleepiness scale was 11.3 ± 7.6 points (table 1).

Thirty-eight participants had hypertension, of these 17 (45%) were untreated, 13 (34%) were treated with angiotensin receptor blockers, 3 (8%) with beta blockers, 12 (32%) with calcium channel blockers, 5 (13%) with diuretics and 1 (3%) patient with alpha-adrenergic blockers.

The hypertensive group (n=38) was older (51 (16.5) vs 43 (13) years, $p=0.008$) and had a higher BMI (37.3 (8.0) vs 32.8 (8.9) kg/m², $p=0.019$) than the normotensive OSA group (n=40). No other baseline differences existed between the two groups (table 2).

Two-week follow up

All 78 patients were seen at two weeks' for follow up. No drop-outs were recorded. For all patients, there was a significant reduction in symptoms, as measured by the ESS (11.0±10.8 vs 7.5±8.0 points, $p<0.001$). The 95th percentile APAP was 13.3±5.0 cmH₂O and air leaks were acceptably low (at 95th percentile 0.30±0.60 L/sec). APAP was used for 14.0±0.0 days and the daily APAP usage was 3.0±2.3 hours/night. 41.0% of patients used APAP for more than 4 hours per night and the total hours of APAP usage over 14 days was 43.3±31.4 hours. There were no differences in compliance data when comparing the hypertensive and normotensive groups (online supplement, table E1).

Absolute blood pressure, blood pressure variability and pulse rate at two-weeks'

Blood pressure variability, as expressed by systolic BP standard deviation (5.3±4.9 vs 4.2±3.4, $p=0.049$), pulse rate (78.0±14.5 vs 75.5±15.8, $p=0.033$) and systolic BP range (10.0±8.8 vs 8.0±6.8, $p=0.040$) decreased following two-weeks' of treatment compared to baseline. There was no difference in absolute BP (systolic and diastolic), diastolic SD or diastolic range (table 1).

Cardiovascular parameter changes – hypertensive vs normotensive participants

A significant change in pulse rate was observed in the hypertensive OSA cohort ($p=0.026$), but not within the normotensive cohort ($p=0.471$, figure E1, table E2, E3). A sub-analysis of patients did not show any impact of compliance on changes of BP or BPV in the two groups but revealed a greater change in the

pulse rate (0.02 ± 8.92 vs -4.44 ± 6.72 bpm, $p < 0.05$) in the group with higher APAP compliance (Table E5).

APAP compliance and BP, BPV

We found that delta mean systolic BP was associated with increased APAP pressure ($r = 0.293$, $p = 0.009$), and delta BPV (systolic standard deviation) was inversely associated with an increased air leak at an APAP 95th percentile ($r = -0.237$, $p = 0.048$). A decrease in the pulse rate (delta pulse) was correlated with an increased number of days when APAP was used for >4 hours ($r = -0.408$, $p < 0.0001$), a lower number of days when APAP was not used ($r = 0.334$, $p = 0.003$), an increase in the total hours of usage ($r = -0.355$, $p = 0.002$), and an increased average daily usage ($r = -0.352$, $p = 0.002$) (Table 3). A regression analyses did not reveal any compliance measures to be independently predict a change in the pulse rate (APAP days used >4 hrs ($p = 0.276$), APAP days not used ($p = 0.695$), APAP total hours used ($p = 0.847$), APAP average daily usage ($p = 0.985$)) (Table 4). When comparing patients with optimal and suboptimal CPAP compliance, there was no difference in the change of the BP (Table E5 and E7), but a reduction in the pulse rate in patients with optimal compliance (-5.50 ± 8.25 vs $-0.50 (10.50)$ bpm; $p < 0.05$).

DISCUSSION

Two-weeks of autotitrating continuous positive airway pressure (APAP) treatment has a beneficial effect on BPV in patients with OSA. This effect seems to occur through modulation of blood pressure variability in the hypertensive patients, most likely due to an improved sympathico-vagal balance.

These results indicate that short-term treatment of OSA with CPAP has a favourable impact on BPV. BPV has a prognostic value on potential future cardiovascular events and this should be considered when assessing patients with OSA and hypertension (21). Although most correlations were modest, this is

not unexpected, as hypertension is a multifactorial condition and multiple factors are contributing significantly.

There is evidence showing that assessing BPV is important when determining the overall cardiovascular risk of a patient with hypertension. Rothwell et al have demonstrated that systolic BPV and maximal systolic BP are strong predictors of stroke, independent of the mean systolic BP (8). An increased residual variability of the systolic BP in patients with treated hypertension is associated with a high risk of vascular events; in comparison, patients with OSA are subjected to repeated surges of sympathetic nervous system activity (22) which explains the higher BPV in these patients (23).

The observed decrease in BPV in patients with OSA treated with APAP is accompanied by a decrease in the pulse rate suggesting a beneficial effect of CPAP on the overall sympathetic activation (24). Heart rate, represented by its surrogate marker pulse rate, can also predict long-term BP changes in patients with OSA treated with CPAP (25) and it could be evaluated in prospective studies of patients with sleep-disordered breathing who are treated with CPAP in clinical sleep services.

Supporting the findings that APAP might influence BP parameters positively, systolic BP changes were associated with an increased APAP pressure. Air leaks are associated with low CPAP compliance (28), and we found that increased APAP leak reduced the effect of the treatment on BPV. This suggests that air leak influences compliance and that it has an indirect haemodynamic effect with a detrimental impact on BPV.

When we compared subgroups with optimal and suboptimal compliance the decreases in BPV parameters did not reach statistical significance, and this

might be due to a small sample size, but it can also be related to the absolute baseline BP values. However, optimal CPAP compliance was associated with a greater reduction in pulse rate, suggesting a greater impact on sympathetic nervous system activation.

Limitations

This was a prospective study but participants were their own controls (pre-post analysis) involving a relatively small cohort, which could potential result in over-estimating the observed effect on BPV. Future investigation into the validity of APAP effect on BPV requires further randomised and controlled studies.

Participants in this study were not assessed using polysomnography, which is the gold-standard for the diagnosis of sleep apnoea (29). However, national and international guidelines state that pulse oximetry is an effective diagnostic test for patients with OSA, and can therefore be used to evaluate patients at moderate and high risk of sleep-disordered breathing (15); routine clinical practice and sparse public health resources have further contributed to the widespread use of nocturnal home pulse oximetries in sleep services.

Office BP measurements might be influenced by the “white-coat effect” (30), a stress-induced rise in BP which occurs when patients are exposed to doctors in the clinical setting. However, as indicated by the Ohasama study, office BP measurements have an important clinical meaning and predict subsequent risk of cardiovascular mortality (31).

Additional information regarding the number of medications used on treated patients may have been useful in determining efficacy of BP control; further, it is important to point out that this study was not powered to compare parameters in the *subgroups* of hypertensive and normotensive patients, but for a pre- vs post-treatment analysis in the whole cohort. Lastly, while only six of our participants

had blood pressures of <120/80 on three separate occasions, future work could focus on the specific differences between normotensive and pre-hypertensive patients (BP >128/80 on three separate occasions.)

CONCLUSION

Two weeks' of treatment with APAP in OSA patients is associated with a significant reduction in BPV, which may reflect the impact of treatment on the sympathetic tone and could be used as a marker for cardiovascular risk assessment. Randomized controlled trials are needed to establish causality and to better understand whether changes in BPV lead to a reduction of cardiovascular events in patients with OSA.

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